Oxygen and angiogenesis: critical factors for the healing of large bone defects

Hans Van Oosterwyck

Biomechanics Section, KU Leuven, Leuven, Belgium
Prometheus, div. Skeletal Tissue Engineering, KU Leuven, Leuven, Belgium

Bone regeneration relies on the revascularization of the defect site, so that cells that contribute to tissue formation are provided with appropriate levels of oxygen. Tissue engineering strategies for the treatment of large, critical sized defects, must therefore among others target angiogenesis. Due to the many influences of oxygen on cell behaviour as well as due to the complex dynamics of bone regeneration (such as e.g. encountered in fracture healing) it is not straightforward to design efficient strategies. In order to support the design of new therapies for the treatment of large bone defects we have developed a computational model that describes the interplay between oxygen, angiogenesis and cell fate in the context of bone regeneration. The model is multiscale in nature, meaning among others that mechanisms taking place at either intracellular, cellular and extracellular scales are considered and coupled. After corroboration to a number of in vivo experiments we have applied the model to explore the efficacy of cellular and growth factor therapies for the healing of a large segmental defect in a mouse model. We found that the efficacy is largely dependent on the host environment (which in the model is translated into quantitative measures of blood vessel number, osteochondrogenic growth factor concentration and progenitor cell number). When comparing the injection of growth factors only, cells only or the combination thereof, simulation results were sometimes counterintuitive and surprising, because of the complex interplay between governing factors. These results provide further (computational) evidence for the fact that (i) host-construct interaction is a determining factor for the successful treatment of large bone defects, (ii) the host environment should be quantified as much as possible in terms of its ‘regenerative potential’ in order to understand (and possibly even predict) the outcome of a certain treatment, (iii) a quantitative, model-based description of host-construct interaction can assist in tailoring a tissue engineering approach in order to make it more successful.

Reference: A. Carlier, L. Geris, K. Bentley et al. MOSAIC: A Multiscale Model of Osteogenesis and Sprouting Angiogenesis with Lateral Inhibition of Endothelial Cells (2012) PLoS Comput Biol, 8(10)

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